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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,880	12/07/2005	Alan Cuthbertson	PN0384	2898

36335 7590 02/19/2008

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
02/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,880	CUTHBERTSON ET AL.	
	Examiner	Art Unit	
	LEAH SCHLIENTZ	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-7 and 9-15* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 11/28/2007, in reply to the Office Action mailed 8/30/2007, is acknowledged and has been entered. Claims 1, 4 and 9 – 11 have been amended. Claims 2 and 3 have been cancelled. New claims 12 – 15 have been added. Claims 1 and 4 – 15 are pending and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments, see pages 5 – 6 of the Response, with respect to the rejection(s) of claim(s) 1 – 7 and 9 – 11 on the ground of non-statutory obviousness-type double patenting over the claims of US 6,264,914; US 6,921,535 and US 7,182,934 have been fully considered. The rejections have been WITHDRAWN as being overcome by amendment.

Applicant's arguments, see pages 6 – 8 of the Response, with respect to the rejection(s) of claim(s) 1, 3 – 7 and 9 – 11 under 35 USC 112 have been fully considered. The rejections have been WITHDRAWN as being overcome by amendment.

Applicant's arguments, see pages 8 – 9 of the Response, with respect to the rejection(s) of claim(s) 1 – 3, 9 and 10 under 35 USC 102(b) as being anticipated by Klaveness *et al.* (US 6,264,914) have been fully considered. The rejections have been WITHDRAWN as being overcome by amendment.

Applicant's arguments, see pages 9 – 10 of the Response, with respect to the rejection(s) of claim(s) 1 – 3, 6, 7 and 9 – 11 under 35 USC 103(a) as being unpatentable over Klaveness *et al.* (US 6,264,914) in view of Archer *et al.* (WO 03/006070) have been fully considered. The rejections have been WITHDRAWN as being overcome by amendment.

Applicant's arguments, see pages 10 – 13 of the Response, with respect to the rejection(s) of claim(s) 1 – 5, 9 and 10 under 35 USC 103(a) as being unpatentable over Klaveness *et al.* (US 6,264,914) in view of Pastan *et al.* (US 2004/0018203) and Arbogast *et al.* (US 7,211,240) have been fully considered. The rejections have been WITHDRAWN as being overcome by amendment.

Applicant's arguments, see page 13 of the Response, with respect to the rejection(s) of claim(s) 1 – 3 and 9 – 11 under 35 USC 103(a) as being unpatentable over Klaveness *et al.* (US 6,264,914) in view of Yang *et al.* (US 6,692,724) have been fully considered. The rejections have been WITHDRAWN as being overcome by amendment.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4 – 7 and 9 – 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim includes the limitation that "L is a linear or branched amino acid comprising biomodifier or linker moiety comprising 1 – 40 amino acid residues and optionally comprising one or more dicarboxylic acid units, ethylene glycol or PEG components, or combinations thereof, provided that a leucine group is linked directly to the group V." However, the specification as originally filed does not provide support that applicant envisaged the full scope of the sub-genus of linker moities which are now claimed. For example, the specification at paragraph 0022 of the published application describe that L is an amino acid-comprising biomodifier or linker moiety. Original claim 3 defines that the amino acid may be from 1 – 40 amino acid residues, and original claim 4 defines that the linker may additionally comprise PEG units, etc. It is acknowledged that compounds disclosed as preferred embodiments in paragraph 0063 of the published application include a few specific examples of compounds having a leucine group directly linked to

group V. However, the disclosure of a few representative examples of linker moities (e.g. Leu-diglycolyl; Leu-Gly—diglycolyl, Leu-Ala-diglycolyl; Leu-Lys(propionyl-PEG(12)-Ac-Diglycolyl) does not provide adequate justification to support the subgenus of linkers which are now claimed, wherein the linker includes any and all possible combinations of 1 – 40 amino acid residues optionally comprising one or more dicarboxylic acid units, ethylene glycol or PEG components, or combinations thereof, with the proviso that a leucine group is linked directly to the group V. For example, compounds having additional amino acids conjugated to group V are also disclosed, as in Table 1. Accordingly, the specification does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 9, 10 and 12 – 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness *et al.* (6,264,914) in view of *Lehninger Principles of Biochemistry* (3rd edition, 2000, p. 119).

Klaveness discloses compositions of the formula V-L-R, where V is an organic group having binding affinity for an angiotensin II receptor site, L is a linker moiety, and R is a moiety detectable in *in vivo* imaging of a human or animal body (abstract). The composition may be used to image cardiovascular diseases and disorders. Losartan is a preferred vector (column 2, line 67; column 3, line 17). Most commonly, the linker comprises two or more reactive moieties connected by a spacer element (column 13, lines 18 – 20). The spacer may be include polyamino acids, homo- and co-polymers of lysine, glutamic acid and aspartic acid, and polypeptides (column 14, lines 21 – 23). See also column 19, lines 39 – 45. The reporter groups include metal radionuclides, such as ^{90}Y, ^{99m}Tc, etc. chelated by chelant groups on the linker moiety (column 23, line 55 – column 25). An exemplified compound is a Tc chelate of N-(N-MAG-3-glycyl)-Losartan (claim 2, compound v).

Accordingly, Klaveness teaches a compound having a glycine amino acid linker, rather than a leucine amino acid linker which is conjugated directly to losartan.

However, it would have been obvious to one of ordinary skill in the art to substitute leucine for glycine as a linking moiety in the compound disclosed by Klaveness when the teaching of Klaveness is taken in view of *Lehninger Principles of*

Biochemistry. Lehninger teaches that Glycine, Alanine, Valine, Leucine, Methionine and Isoleucine are classified as amino acids having non-polar aliphatic R groups (see Table, page 119).

The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143. In the instant case, the substituted components (leucine and glycine) and their functions were well known in the art at the time of the instant invention. One of ordinary skill in the art could have substituted one known amino acid classified as having a non-polar aliphatic R group for another, and the results of such a conservative substitution would have been predictable, that is a structurally similar compound having a chelating moiety effectively linked to losartan via a functionally equivalent amino acid for use as a radiopharmaceutical.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness *et al.* (6,264,914) in view of *Lehninger Principles of Biochemistry* (3rd edition, 2000, p. 119), as applied to claims 1, 9, 10 and 12 – 14 above, in further view of Yang *et al.* (US 6,692,724).

Klaveness discloses compositions of the formula V-L-R, as set forth above, but does not specifically teach a kit comprising the ligand-chelate conjugate and a reducing agent.

Yang discloses ^{99m}Tc chelates which are conjugated to a variety of ligands for tissue-specific imaging. Kits for the use in tissue-specific disease imaging are also provided (abstract). Kits are provided for preparing a radiopharmaceutical preparation. The kit generally includes a sealed via or bag, or any other kind of appropriate container, containing a predetermined quantity of an ethylenedicysteine-tissue specific ligand conjugate composition and a sufficient amount of reducing agent to label the conjugate with ^{99m}Tc. In certain cases, the ethylenedicysteine-tissue specific ligand conjugate composition will also include a linker between the ethylenedicysteine and the tissue specific ligand. The tissue specific ligand may be any ligand that specifically binds to any specific tissue type (column 4, lines 25 – 40).

The rejection over Klaveness in view of *Lehninger Principles of Biochemistry* is applied as above. It would have been further obvious to one of ordinary skill in the art at the time of the instant invention to provide the compositions of Klaveness in view of Lehninger in the form of a kit comprising a reducing agent because both Klaveness and Yang teach targeted ^{99m}Tc chelates, and because Yang teaches that such reducing agents are useful in kits for providing radiopharmaceutical preparations (column 4, lines 25 – 40). One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Yang teaches a reducing agent, such as

stannous chloride to be important for the reduction of Tc to its 4+ oxidation state (column 8, lines 49 – 64).

Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness *et al.* (6,264,914) in view of *Lehninger Principles of Biochemistry* (3rd edition, 2000, p. 119), as applied to claims 1, 9, 10 and 12 – 14 above, in further view of Archer *et al.* (WO 03/006070).

Klaveness discloses compositions of the formula V-L-R, as set forth above. A variety of chelating agents are taught to be suitable for binding the radionuclude, but Klaveness does not specifically teach those of formula II, as claimed in instant claims 6 and 7.

Archer teaches improved chelator conjugates with biological targeting molecules, suitable for forming metal complexes with radiometals, which are useful as radiopharmaceuticals, especially with ^{99m}Tc (abstract). Such chelators include those such as in Formula II, wherein Y is $-(A)_n-X-Z$. A_n is a linker moiety, such as CR_2, where R is H, C_{1-10} alkyl, etc.; X is NR^4, etc.; and Z is a biological targeting moiety, including synthetic receptor-binding compounds, etc. (page 4). The radiometal complexes may be prepared by reacting a solution of the radiometal in the appropriate oxidation state with the chelate conjugate at the appropriate pH, and may include the addition of a reducing agent (page 14, lines 1 – 15).

The rejection over Klaveness in view of *Lehninger Principles of Biochemistry* is applied as above. It would have been further obvious to one of ordinary skill in the art at

the time of the instant invention to substitute the diaminedioxime chelators taught by Archer as the chelating agent employed in the V-L-R compounds taught by Klaveness in view of Leninger. Klaveness teaches that a variety of chelating agents may be employed to bind a radionuclide. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so, because the diaminedioxime chelators are taught in the prior art to be functional equivalents for use in binding radionuclides, as shown by Archer.

Claims 4, 5 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness *et al.* (6,264,914) in view of *Lehninger Principles of Biochemistry* (3rd edition, 2000, p. 119), as applied to claims 1, 9, 10 and 12 – 14 above, in further view of in view of Pastan *et al.* (US 2004/0018203) and Arbogast *et al.* (US 7,211,240).

Klaveness discloses compositions of the formula V-L-R, as set forth above. A variety of linker moieties may be used, but Klaveness does not specifically teaches pegylated amino acids or branched amino acids.

Pastan discloses compositions comprising a targeting moiety linked to an effector molecule through a connector molecule, which connector molecule comprises one or more polyethylene glycol molecules. The targeting molecule may be a ligand, etc. (paragraph 0013). The connector molecule is a peptide (paragraph 0018). The effector molecule may be a radionuclide, a detectable label, etc. (paragraph 0020). Conjugation of PEG to a peptide linker provides increased circulation time, etc. (paragraph 0033 – 0034).

Arbogast discloses multivalent constructs which bind to a targeting agent (column 5, lines 20+). Such constructs include a diagnostic or therapeutic moiety chelated to a chelating moiety, such as a radionuclide (column 6, lines 5+). The chelators may be linked to a targeting moiety via a variety of linkers, including linear, branched, or cyclic amino acids (column 42, lines 54 – 56).

The rejection over Klaveness in view of *Lehninger Principles of Biochemistry* is applied as above. It would have been further obvious to one of ordinary skill in the art at the time of the instant invention to provide pegylated amino acids or peptides as the linker in the composition of Klaveness in view of Lehninger. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Pastan discloses that conjugation of PEG to a peptide linker provides increased circulation time, etc. such as in linkers to which PEG is conjugated to a peptide linker and metal chelates (paragraph 0033 – 0034). It would have been further obvious to utilize branched amino acids as the linker because Klaveness teaches that a variety of linking moieties can be used, including various amino acid and peptide linkers, and because Arbogast shows that linear, branched, etc. amino acids are well-known in the art for linking chelating moieties to a chelating agent.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 9, 10 and 12 – 14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 4 of U.S. Patent No. 6,264,914 in view of *Lehninger Principles of Biochemistry* (3rd edition, 2000, p. 119). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to compositions of formula V-L-R wherein V is an organic group having binding affinity for an angiotensin II receptor, L is a linker moiety, and R is a reporter moiety. The reporter moiety includes radionuclides conjugated to a chelating ligand; the linkers include amino acids; and the compounds are used for methods of imaging a human or animal subject.

The '914 patent includes a compound having a glycine amino acid linker, rather than a leucine amino acid linker which is conjugated directly to losartan.

However, it would have been obvious to one of ordinary skill in the art to substitute leucine for glycine as a linking moiety in the compound disclosed by Klaveness when the teaching of Klaveness is taken in view of *Lehninger Principles of*

Biochemistry. Lehninger teaches that Glycine, Alanine, Valine, Leucine, Methionine and Isoleucine are classified as amino acids having non-polar aliphatic R groups (see Table, page 119). One of ordinary skill in the art could have substituted one known amino acid classified as having a non-polar aliphatic R group for another, and the results of such a conservative substitution would have been predictable, that is a structurally similar compound having a chelating moiety effectively linked to losartan via a functionally equivalent amino acid for use as a radiopharmaceutical. Accordingly, the claims are overlapping in scope and are obvious variants of one another.

Claim Objections

Claim 8 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LEAH SCHLIENTZ whose telephone number is (571)272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618